REMARKS

Claims 1-6, 37 and 45 and new claims 46-47 are active. The specification and claims have been amended for clarity. Claims 46 and 47 find support in original claim 1 and on pages 6, 7, 12 and 13 of the specification. No new matter is believed to have been introduced. Favorable consideration of these amendments and allowance of the case are respectfully requested.

Restriction/Election

The Applicants previously elected with traverse **Group I**, claims 1-6, 37 and 45, directed to a method of identifying ligands or aptamers. The requirement has been made FINAL. The Applicants respectfully request that the claims of the nonelected group(s) or other withdrawn subject matter which depend from or otherwise include all the limitations of an allowed elected claim, be rejoined upon an indication of allowability for the elected claim, see MPEP 821.04.

Objections—Specification

The specification was objected to as containing active hyperlinks and page 41 as not identifying sequences using a sequence identifier. These issues are moot in view of the amendments above.

Rejection—35 U.S.C. §112, first paragraph

Claims 1-6, 37 and 45 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate enablement with respect to methods using cells other than Pc12 cells, see page 5, 2nd paragraph of the rejection. Thus, while the Examiner acknowledges that the inventors possessed a method involving PC12 cells expressing a Ret receptor mutated in the intracellular and extracellular domains and contacting the cells with a modified library of 2-F-py-RNAs, she is

concerned that the inventors did not describe so as to enable a method applied to any mutated RPTK, any cell type, or any library.

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989), see MPEP 2163.02.

Claim 1 step (a) refers to "cells not expressing said receptor protein-tyrosine kinase or expressing it in a nonactivated form (C_N cells), said cells having a same cell type as cells expressing a same receptor protein-tyrosine kinase but in an activated form, due to existence of a mutation in an extracellular domain of said receptor protein-tyrosine kinase (C_{Te} cells)". This language finds express support in original claim 1 and on pages 6 and 7 of the specification.

The concern was that no description was provided for other cell types containing tyrosine kinase receptor proteins having intracellular or extracellular mutations. These concerns are misplaced for the following reasons. It was well within the skill of those in the art, which is generally recognized as post-doctoral level, to practice the method of the invention with other cell types, other mutated RPTK and other starting mixtures of nucleic acids. Mutations in tyrosine kinase receptor proteins could have been easily localized to the intracellular or extracellular domains using conventional techniques and it would have been well within the skill of the art to identify cells not expressing tyrosine kinase receptors or such receptors in inactive form.

The attached references—Ohuchi, et al. (2006) and Chen, et al. (2009) show that one of skill in the art would have been enabled to easily implement the claimed method for other cell types, other kinds of RPTK receptor proteins, and other starting mixtures of nucleic acid sequences.

Ohuchi, et al. teach obtaining RNA aptamers recognizing transforming growth factor-β type III receptor. (i.e., a RPTK different from Ret) expressed by Chinese hamster ovary cells, see the abstract. Moreover, Ohuchi, et al. related their method to that of the invention at page 7, right col. (at the end of the paragraph before the Acknowledgments):

> Following the completion of all experiments described here, we became aware of a recent study that reported the isolation of RNA aptamers against human receptor tyrosine kinase RET using RET-expressing cells as targets in a modified SELEX procedure similar to TECS-SLEX [15][1].

Chen, et al. teach obtaining single-stranded DNA (ssDNA) aptamers recognizing the HCV E2 envelop glycoprotein expressed by CT26 cells from a starting mixture of ssDNA, see page 2, the paragraph bridging the left and right columns, thereby showing that such a method can be extended to targets even beyond the RPTKs to all types of cells capable of expressing the target and to starting nucleic acid mixtures different from 2'-flouropyrimidine RNAs.

Consequently, the present disclosure describes and enables the invention and this rejection cannot be sustained.

Rejection—35 U.S.C. §112, second paragraph

Claims 1-6, 37 and 45 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. These rejections are moot in view of the amendments above.

Rejection—35 U.S.C. §103(a)

Claims 1-6, 37 and 45 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chen, PNAS 10:9226 in view of Yayon, et al., U.S. Patent No. 7,498,416. This rejection cannot be sustained because the cited references do not suggest and provide a reasonable expectation of success for the invention.

[1] Reference [15] is Cerchia, et al., (2005) PLos Biol. 3:e123.

Chen was relied upon for teaching a method of identifying RNA aptamers against RPTKs. Chen refers to aptamers that inhibit the signaling function of hergulin (a RPTK) that has ***an isolated extracellular domain*** of HER3 which was recombinantly produced, see *Production of HER3ECD* and *SELEX* portions of the *Materials & Methods* section on page 9227.

The Examiner acknowledges on page 12, lines 3-5 that "Chen does not teach that the tyrosine kinase receptor, HER3 is mutated at the extracellular and intracellular region".

Yayon was relied upon as a secondary reference teaching that "other screens can be carried out on cell lines expressing a RPTK mutation". However, Yayon are primarily directed to ***antibodies*** or ***antibody fragments*** against the extracellular domain of FGFR3 and involve applying an antibody selection method, that is, using a dimeric soluble form of FGFR3 to the soluble extracellular domains of an RPTK, such as Ret, see col. 7, lines 10-19 and col. 10, lines 44-60. Yayon further suggest that antibodies could be screened with cell lines expressing a mutated RPTK, such as the FDCP-FR3ach cell line, see col. 24, lines 55-60.

One of ordinary skill in the art at the time of invention would have not looked to Yayon or considered its antibody-related teachings with respect to methods for screening aptamers from a starting mixture of nucleic acids. To emphasize this difference the present claims have been directed to aptamers and omit the term "ligands".

Moreover, neither Chen, nor Yayon provided any motivation for screening aptamers against ***RPTKs expressed by cells***. Yayon teaches away from this because it expressly indicates that the target for screening antibodies against Ret should be a ***soluble*** extracellular domain of Ret.

Furthermore, one of ordinary skill in the art would not have had a reasonable expectation of success for successfully implementing a method for selecting aptamers specifically directed to a RPTK by using cells modified to express RPTK since the prior art did not show that specific

aptamers could in fact be screened using cells modified to express a membrane protein of any type. Indeed, one of ordinary skill in the art would have expected that in view of the usual feeble expression rate of membrane proteins by cells modified to express a membrane protein that too few putative aptamers would have been selected at each round of selection to yield a true aptamer specifically binding to the target.

Chen in combination with Yayon also do not disclose or suggest all the elements of the invention required by the present claims, that is, recovering the putative aptamers which don't bind to either cells not expressing the RPTK (C_N cells) or to cells which express RPTK mutated in its intracellular portion (C_i cells). Consequently, for all of these reasons this rejection cannot be sustained.

Conclusion

In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. An early notice to that effect is earnestly solicited.

Respectfully submitted,

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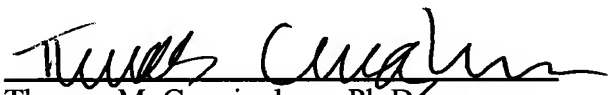

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